REMODELLING OF EXTRACELLULAR MATRIX IN RECTAL CANCER AND PREOPERATIVE RADIOTHERAPY

AKADEMISK AVHANDLING

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av

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Avhandlingen baseras på följande delarbeten:

I. Matrix metalloproteinases in rectal mucosa, tumour and plasma: response after preoperative irradiation.
Angenete E, Langenskiold M, Falk P, Ivarsson ML,
Int J Colorectal Dis 2007;22(6):667-74

II. Transforming growth factor beta-1 in rectal tumour, mucosa and plasma in relation to radiotherapy and clinical outcome in rectal cancer patients.
Angenete E, Langenskiold M, Palmgren I, Falk P, Oresland T, Ivarsson ML,
Int J Colorectal Dis 2007;22(11):1331-8

III. uPA and PAI-1 in Rectal Cancer-Relationship to Radiotherapy and Clinical Outcome.
Angenete E, Langenskiold M, Palmgren I, Falk P, Oresland T, Ivarsson ML,
J Surg Res 2008 Apr 7 (Epub ahead of print)

IV. Preoperative radiotherapy and extracellular matrix remodelling in rectal mucosa and tumour. Matrix metalloproteinases and plasminogen components
Angenete E, Öresland T, Falk P, Breimer M, Hultborn R, Ivarsson ML,
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ABSTRACT

BACKGROUND

Preoperative radiotherapy reduces local recurrence due to rectal cancer, but increases postoperative morbidity. The aim of this thesis was to study the impact of radiotherapy on extracellular matrix (ECM) remodelling enzymes and growth factors after radiotherapy and also their possible use as surrogate markers for complications. A secondary aim was to explore the use of these enzymes and growth factors as markers for tumour classification and risk predictors of metastases and death of rectal cancer.

MATERIALS AND METHODS

In paper I-III 91-110 patients undergoing surgery with or without preoperative radiotherapy were studied through biopsies taken from tumour tissue and adjacent mucosa as well as plasma samples during surgery. Clinical parameters were registered and the patients were followed yearly. Paper IV encompasses 32 patients with sequential biopsies before treatment and from the surgical specimen. Twenty of them received preoperative radiotherapy. Protein levels of matrix metalloproteinase (MMP)-1, -2, -9 (Papers I and IV), urokinase plasminogen activator (uPA) (Papers III-IV), plasminogen activator inhibitor-1 (PAI-1) (Papers III-IV), transforming growth factor-β1 (TGF-β1) (Papers II and IV), tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) (Paper IV) and calprotectin (Paper IV) were determined by ELISA. Biopsies from irradiated and non-irradiated peritoneal areas were also analysed (Paper IV) for tissue-type plasminogen activator (tPA). The localisation of calprotectin in mucosa was determined by immunohistochemistry (Paper IV).

RESULTS

MMP-2 and PAI-1 levels were higher after radiotherapy in both mucosa and tumour whereas uPA and calprotectin were higher in mucosa after radiotherapy. High levels of MMP-2 correlated to wound-infections and fistula formation. Peritoneal biopsies displayed lower levels of tPA in irradiated patients indicating a reduced fibrinolytic capacity. Levels of MMP-1, -2, -9, uPA, PAI-1, total TGF-β1 and calprotectin were higher in tumour tissue compared to mucosa. High levels of total TGF-β1 in tumour tissue correlated to the presence of metastases and high levels of PAI-1 in tumour tissue were associated with lateral spread irrespective of radiotherapy. PAI-1 in tumour tissue was also associated with an increased risk of death due to rectal cancer in multivariate analysis.

CONCLUSIONS

The ECM remodelling proteases and growth factors mirror to some extent the response to radiotherapy and may be involved in the pathogenesis of radiotherapy associated morbidity. MMP-2 can be related to clinically evident complications after surgery and radiotherapy and could be explored further for use as a clinical marker. To further improve selection of patients for radiotherapy the levels of TGF-β1 and PAI-1 in tumour tissue could be of use in preoperative assessment.

Keywords: Rectal cancer, Radiotherapy, Extracellular matrix, MMP-2, PAI-1, uPA, Calprotectin, TGF-β1

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